Importation of Active Pharmaceutical Ingredients (APIs) Requirements
7-16-08 FDA NYK-DO API Seminar Presentation Notes (Tab A)

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A. DEFINITIONS:

1. "Drug" [FD&C Act Section 201(g)(1)]:

- Articles intended to diagnose, cure, mitigate, treat or prevent disease in man or other animals

- Articles (other than food) intended to affect the structure or any function of the body of man or other animals

- Articles intended for use as a component of a drug

2. "New" drug [FD&C Act Section 201 (p) & 505]:

- "any drug.... the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience...., as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling."

- A "new drug" must be covered by an approved new drug application (NDA/ANDA) to be marketed in the U.S. or by an investigational new drug application (IND)

- Applies to both Rx and OTC drugs

3. Over-the-counter drug products (OTC):

- All other drugs that can be used safely without medical supervision

  Example: Medications for fever such as aspirin and acetaminophen, preparations for the common cold or allergies, antacids, and some first aid antibiotics

4. Prescription (Rx) drug products (Rx) [FD&C Act Section 503(b)(1)]:

- These drugs cannot be used safely without medical supervision

Example: Injectable drugs or drugs to treat serious conditions like heart disease, cancer, or fertility problems

5. Active Pharmaceutical Ingredient (API) *a.k.a. bulk drug substance* [21 CFR 207.3]

- "any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug“

- "term does not include intermediates used in the synthesis of such substance"

6. Adequate Directions for Use [21 CFR 201.5]: “directions under which a layman can use the drug safely….”

B. REGISTRATION & LISTING:

1. Requirements for Foreign Establishments:

- FFDCA Section *510(i)* [21 U.S.C. 360]
- *21 CFR 207.40*
- FFDCA Section *502(o)* [21 U.S.C. 352]
- FFDCA Section *801(o)* [21 U.S.C. 381]

2. Foreign firms that manufacture, prepare, propagate, compound, or process a drug imported or offered for import into the U.S. are required to…

a. Register name and place of business

b. List all drugs imported or offered for import into the U.S.

c. Designate a U.S. Agent
- Each foreign drug establishment shall designate only <u>one</u> United States agent
- <u>Must</u> be physically located in the U.S.
- Point of contact between FDA and foreign firm on all drug registration & listing matters and requirements
- Letter of designation must:
  - Be prepared on the foreign firm's letterhead
  - Signed by authorizing official of the firm
  - Contain: Name of the firm's designated U.S. Agent, Address, Telephone/ fax numbers, and E-mail address

3. Registration must be renewed annually

4. Registration required before any application is approved

5. Listing information must be updated:
   a. Every June and December or
   b. Discretion of the registrant or
   c. When any change occurs

6. National Drug Code Number (NDC #):
   a. Assigned to each listed product
   b. Identifies manufacturer/distributor, drug, and trade package size/type
   c. FDA requests but does not required to appear on the product label or labeling:
      - If the NDC # appears on the label it must comply with *21 CFR 207.35 (b)(3)*

7. <u>Does *not*</u> indicate FDA's approval of a firm or its products

8. The Bioterrorism Act of 2002:
   Requires foreign drug establishments whose drugs are imported into the U.S. to submit certain information with the annual registration (This is in addition to the regular registration requirements):

   - Each importer/consignee of each drug in the U.S. known to the manufacturer at time of registration
   - Each person who imports or offers to import the manufacturer's drugs
   - The name and contact information of U.S. Agent

9. Non-listed products are misbranded [*502(o)]* & in violation of *801(a)(3)*

10. Firms that are not in compliance with *510(i)* are in violation of *801(o)*

11. Listing Requirements – Exemptions:
   a. Inactive ingredients
   b. Intermediates (non-API)
   c. Drug products not for importation into the U.S.
   d. Drugs imported or offered for import under an Investigational New Drug Application (IND) [*21 CFR 312*]
   e. Components of drugs imported under 801(d)(3) - Import for Export (IFE)

12. Information:

a. FDA Forms: www.psc.gov/forms
b. NDC Directory: www.fda.gov
c. Guidance Annual Registration: www.fda.gov/cder/drls/registration_listing.htm
d. Annual Registration Status: www.fda.gov/cder/dfars/default.htm
e. Registration & Listing contact number: 301-210-2840
f. Draft Guidance: E-Registration & Listing: FRN Vol. 73, No. 134, 7/11/08, Page 39964

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ``Providing Regulatory Submissions in Electronic Format--Drug Establishment Registration and Drug Listing." This draft guidance document establishes a Pilot Program for industry to voluntarily submit drug establishment registration and drug listing information in an electronic format that FDA can process, review, and archive. The document provides guidance on what required and FDA-recommended information related to drug establishment registration and drug listing to submit and on how to electronically prepare and submit the information to FDA.

C. API EXEMPTIONS:

1. 21 CFR 201.122(a):

a. API is intended for use in a product **approved** in a NDA, ANDA, or supplement
b. API is manufactured by the supplier approved in the new drug application
c. Prescription (Rx) and over-the-counter (OTC) drugs covered by an approved application
d. Labeling (Must):
   - "Caution: for manufacturing, processing, or repacking" &
   - "Rx only"- when most dosage forms in which the API may be used are subject to prescription *[503(b)(1)]*
e. Useful Information:
   - API product name and NDC number
   - Name and address of the API manufacturer
   - Number of approved NDA/ANDA or supplement
   - Finished dosage drug product name and NDC number

2. 21 CFR 201.122(b):

a. API is intended for use in a product **subject** to an IND (for clinical use)
b. Must be covered by an active IND
c. Must be going to person(s) authorized in the IND
d. Labeling (Must):
   - "Caution: for manufacturing, processing, or repacking in the preparation of a new drug or new animal drug limited by federal law to investigational use"

e. Useful Information:
   - IND number
   - Sponsor's name
   - Name of the product

3. 21 CFR 201.122(c):

a. API is intended for use in a product subject to a **pending** NDA or ANDA or supplement
b. API is manufactured by the supplier included in the pending NDA, ANDA, or supplement.
c. Applies to prescription (Rx) and over-the-counter (OTC) drugs
d. Labeling (Must):
   - "Caution: for manufacturing, processing, or repacking" &
   - "Rx only"- when most dosage forms in which the API may be used are subject to prescription *[503(b)(1)]*

e. Useful Information:
   - API product name and NDC number
   - Name and address of the API manufacturer
   - Number of pending NDA/ANDA or supplement
   - Finished dosage drug product name and NDC number (if applicable)
   - Written commitment that products manufactured with the API will not be introduced in commercial distribution until they are approved

4. 21 CFR 201.125:

a. API is intended for use in teaching, law enforcement, research, and analysis
b. Includes both APIs and finished drug products
c. Cannot be used in human research
d. API product name and NDC number
e. Name and address of the API manufacturer
f. Name and address of U.S. Consignee
g. Written commitment that the quantity offered for import is reasonable for the contemplated research, teaching, analysis, etc.

5. 21 CFR 312.160:

a. API is intended for **investigational (IND) use** in laboratory research animals or in-vitro testing
b. To conduct R&D work prior to the submission of an IND
c. Product cannot be used in humans
d. Must comply with all the requirements under *21 CFR 312.160*
e. Includes both APIs and finished drug products
f. Labeling (Must):
- "Caution: Contains a new drug for investigational use only in laboratory research animals, or for tests in-vitro. Not for use in humans"

g. Useful Information:
- API product name
- Name and address of API manufacturer
- API label content demonstrating compliance with *21 CFR 312.160*

D. MISBRANDING - Adequate Directions for Use *[502(f)(1) & 21 CFR 201.5]*: "directions under which a layman can use the drug safely"

1. All drugs, including APIs, must bear "adequate directions for use" or meet one of the **exemptions**. If not, then **misbranded** [*502(F)(1)*].

2. Only **OTC** finished drug products can meet this requirement. All other drugs must meet one of the exemptions

E. MARKETING – REQUIREMENTS & USEFUL INFORMATION:

1. OTC pending and final monograph drugs:

a. Labeling (Must):
- "Caution: for manufacturing, processing, or repacking"

b. Useful Information:
- Name and NDC # of product to be manufactured with the API
- A statement justifying why an approval is not required for the finished drug product
- API label content demonstrating compliance with *21 CFR 201.122*

2. Pharmacy Compounding

a. Labeling (Must):
- "For Prescription Compounding"
- "Rx only"

b. Useful Information:
- API is a component of an FDA approved drug
- API meets official compendial requirements when applicable
  Example: Certificate of Analysis
- Drug has not been withdrawn or removed from the U.S. market for public health reasons (list in *CPG 460.200*)
- API product name and NDC #
- Name of API manufacturer and registration number
- A written commitment that the API will be sold and used solely for pharmacy compounding by a state licensed pharmacy or federal facility
- A written commitment that the drug has not been withdrawn or removed from the U.S. market for public health reasons

3. Pre-Submission Batches: (Batches used to conduct the studies necessary to generate data required to submit an application or supplement
Example: Bioequivalence, bioavailability, and stability batches)

a. Useful Information:
- API product name and NDC #
- Name and address of the API manufacturer
- Name and address of U.S. consignee
- Product must be labeled as per *21 CFR 201.122*
- For supplements - may include number of NDA/ANDA to be supplemented and NDC # of finished product

b. Written commitment that product manufactured with API will not be introduced in commercial distribution until approved

c. Explanation that API is intended to generate data to submit an application/ supplement
Example: Bioequivalence and/or bioavailability batches

4. Prescription (Rx) drugs not currently subject to application requirements:

a. Labeling (Must):
   - "Caution: For manufacturing, processing, or repacking"
   - "Rx only"

b. Useful Information:
   - Name and NDC # of product to be manufactured with the API
   - A statement justifying why an approval is not required for the finished drug product
   - API label content demonstrating compliance with *21 CFR 201.122*

F. DATABASES:

1. **Drug Master Files (DMFs):**
   a. Contain API chemistry and manufacturing control information
   b. Are submitted to FDA voluntarily by the API manufacturer
   c. NDA/ANDA sponsors may elect to refer to a an API DMF in their application
   d. Are not approved by FDA
   e. They are reviewed by FDA in reference to a submission and are judged to be either adequate or inadequate with regard to that submission
   f. May be referenced in multiple applications
   g. May be associated with both approved and unapproved applications
   h. A DMF number is not sufficient to show that the API supplier is approved in an application

2. **Establishment Evaluation System (EES):**
   a. Confirming Application Information
   b. Automated tracking system
   c. Originally for tracking status of establishments in drug applications submitted for FDA approval
   d. Approval is site specific - currently used to verify that imported APIs are from approved sources in the application
   e. Launched in 1996
   f. Has specific site information from 1992 to the present
   g. Specific information for each application prior to 1992 is not accessible
   h. Useful Information – API Information not in EES:
      1) For APIs included in original or initial application:
         - Copy of the documents from original submission showing the supplier of the API
           Example: CMC information with drug substance information

- Must explain any discrepancies - change in name, etc.
- FDA Approval Letter

2) For APIs included in a supplement:
   - Copy of the official FDA letter approving the supplement and covering the API supplier
   - Must explain any discrepancies - change in name or address

G. Pre-Launch Activities Importation Request (PLAIR):

H. CONTACTS: CDER Import & Export Team Members:

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